The Examiner has requested that the title be amended to be more descriptive. Claims 13 and 14 stand rejected under the judicially created doctrine of obviousness-type double patenting over claims 5 and 7 of USPN 6,083,906. Claims 13 and 14 stand rejected under 35 U.S.C. §112, first paragraph, and claim 14 has been rejected under 35 U.S.C. §112, second paragraph. And, claims 13 and 14 stand rejected under 35 U.S.C. §102(a). Applicant will address each of these issues in the order presented in the Office Action.

Applicant cites two abstracts in the arguments below: McDaniel, M.L., *et al.*, *Proc. Soc. Exp. Med.*, 1996, 211(1): 24-32 and Singer I.I., *et al.*, *Gastroenterology*, 1996, Oct;111(4):871-85. Applicant was not able to procure copies of the references at the time of filing this response and assures the Examiner that copies of the full references will be forwarded as soon as possible. Applicant thanks the Examiner in advance for his patience in this matter.

The specification has been amended to correct an obvious error at page 4. The specification has been corrected to properly refer to SEQ ID NO:3 for *human* IL-17R. Support for the amendment may be found at page 4, lines 17-18. Additionally, two misspellings have been corrected at page 16. Claim 13 has been amended to specify a method of treating a mammal afflicted with ulcerative colitis, the method comprising administering to said animal an effective amount of a soluble Interleukin-17 Receptor (IL-17R) protein and a pharmaceutically acceptable diluent or carrier.

Claim 14 has been amended to specify that the IL-17R is a soluble IL-17R and reference to the GAP algorithm has been removed. Support for soluble IL-17R molecules may be found in the specification, for example, at page 4, lines 6-27.

Applicant has added claims 15 and 16, which are drawn to a method of treating diabetes and claims 17 and 18, which are drawn to methods of treating Crohn's disease. The subject matter of claims 15-18 were originally found in claim 13 and are fully supported by the specification as originally filed.

Formal Matters:

The Examiner has requested Applicant to amend the title in order to more closely reflect the claimed invention. Applicant requests that this issue be held in abeyance until claims have been allowed in order for Applicant to accurately amend the title.

Double Patenting:

Claims 13 and 14 stand rejected under the judicially created doctrine of obviousness-type double patenting over claims 5 and 7 of USPN 6,083,906. The

Examiner states that inclusion of the phrase "preventing" in claim 13 reads on claim 5 of USPN 6,083,906. Applicant has amended claim 13 to remove the term "preventing" in order to expedite allowance of the claims. As such, the Examiner's basis for obviousness-type double patenting has been eliminated and the rejection may be properly withdrawn. Applicant notes that removal of the term "preventing" is not construed as a narrowing amendment. In addition, Applicant has amended claim 13 to distinguish the method steps from those of USPN 6,083,906 by specifying the patient population being treated.

35 U.S.C. §112, second paragraph

Claim 14 has been rejected as being indefinite for reciting the limitation pertaining to "the GAP computer program" because the Examiner believes it is unclear what the GAP computer program is. Applicant respectfully disagrees. The specification teaches at page 10, lines 15-20 that the GAP computer program is described by Devereux, et al. in *Nucleic Acid Research* 12:387. Applicant submits that one of skill in the art would be familiar with this well-established program and would also understand that similar and more updated methods may be used to analyze homologs of IL-17R (as stated at lines 19-20 of page 10). Nevertheless, Applicant has amended the claims to delete reference to the algorithm in order to expedite prosecution. Applicant notes that removal of the algorithm is not construed as a narrowing amendment.

35 U.S.C. §112, first paragraph

Claims 13 and 14 stand rejected under 35 U.S.C. §112, first paragraph as containing subject matter that was not described in the specification in such a way as to enable one skilled in the art to use the claimed invention. Applicant respectfully disagrees and requests the Examiner to reconsider this issue in light of the following information.

In short, the Examiner asserts that due to the unpredictability of the art, undue experimentation would be required in using the claimed invention. In support of this argument, the Examiner notes that IL-17 stimulates production of NO in cartilage-associated cells in OA and therefore treating OA with IL-17R would be a "useful" therapy. But, the Examiner has doubts about the predictability of treating diabetes, ulcerative colitis and Crohn's disease because release of NO may be promoted by factors other than IL-17, such as IL-1β, TNF-α, LPS and INF-γ. The Examiner states that neither the prior art nor the present disclosure has demonstrated an association of IL-17 to diabetes, ulcerative colitis and Crohn's disease, and therefore, in the absence of predictability of involvement of IL-17 in said diseases, it is unpredictable that the treatment of the diseases with soluble IL-17R would be predictable. As a result, the

Examiner believes undue experimentation would be required to practice the claimed invention.

The test of enablement is whether one skilled in the art could make or use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation. *United States v. Telectronics, Inc.*, 857 F.2d 778, 8 USPQ2d 1217 (Fed. Cir. 1988); *In re Stephens*, 529 F.2d 1343, 188 USPQ 659 (CCPA 1976). The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d 498, 190 USPQ 214 (CCPA 1976). The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *M.I.T. v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985).

The "predictability or lack thereof" in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. If one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change within the subject matter to which that claimed invention pertains, then there is lack of predictability in the art. Accordingly, what is known in the art provides evidence as to the question of predictability.

In response, Applicant will show that IL-17 plays a role in the pathophysiology of diabetes, ulcerative colitis and Crohn's disease, and therefore, treating such diseases with IL-17R would not require undue experimentation. Also, Applicant will show that undue experimentation would not be required to administer IL-17R to an individual.

IL-17 has been shown to simulate the production and expression of, *inter alia*, IL-1β and TNF-α by human macrophages. (Jovanovic, D.V., *et al.*, *J Immunol*, 1998, Apr 1;160(7):3513-21). It is known in the art that IL-1β, TNF-α, LPS and INF-γ induce formation of NO in a number of cells through receptor-mediated tyrosine kinase activation and activation of one or more transcription factors, such as NF-κB, leading to mRNA iNOS transcription and eventual release of NO (Vladutiu, *Clin Imm and Immunopath*, 1995, 76:1, 1-11, pg. 2, left col., of record). With regards to diabetes, cytokines released by activated macrophages, such as IL-1, have been implicated as immunological effector molecules that both inhibit insulin secretion from the pancreatic beta cell and induce beta-cell destruction. Recent findings have demonstrated production of NO mediates these deleterious effects (abstract by McDaniel, M.L., *et al.*, *Proc. Soc. Exp. Med.*, 1996, 211(1): 24-32). With regards to inflammatory bowel diseases, studies have shown that iNOS expression was localized to the inflamed colonic epithelium in

ulcerative colitis, Crohn's disease and diverticulitis, but not in uninflamed epithelium (abstract from Singer I.I., *et al.*, *Gastroenterology*, 1996, Oct;111(4):871-85). Together these studies demonstrate that IL-17 is directly implicated in the pathway leading to increased NO release and associated pathology in diabetes, ulcerative colitis and Crohn's disease. Therefore, IL-17R may be used to limit the effect of IL-17 on the production of IL-1β and TNF-α, which in turn would reduce the formation of NO and thereby limiting the pathology associated with NO.

Applicant has shown that IL-17 is directly implicated in the immunopathology of diabetes, Crohn's disease and ulcerative colitis, and as such, undue experimentation would not be required to administer IL-17R to patients suffering from those diseases. Thus, the Examiner's basis for claiming a lack of predictability is not supported by the art and the rejection should be properly withdrawn.

Next, the Examiner objects to the claim language "preventing" an inflammatory disease. While Applicant does not acquiesce to the Examiner's characterization, the term "preventing" has been deleted in order to expedite early allowance of the claims. Applicant notes that removal of this additional claim limitation is not considered a narrowing amendment.

The Examiner states that the recitation in claim 13 of "administering an effective amount of an interleukin-17 receptor" reads on the full-length molecule of the IL-17R. Applicant has amended the claim to specify a *soluble* interleukin-17 receptor. Support for soluble IL-17R proteins may be found, for example, in the specification at page 4, lines 6-27.

The Examiner asserts that it would require undue experimentation to practice parts (c) and (d) of claim 14 for reasons of record. Applicants respectfully disagree. Applicant notes that the "first paragraph of 35 U.S.C. §112 requires nothing more than objective enablement; how such a teaching is set forth, either by use of illustrative examples or by broad terminology, is of no importance." *(In re Marzocchi and Horton*, 169 USPQ 364; CCPA 1971).

Applicant discloses the polynucleotide and amino acid sequences for human and murine IL-17R (see sequence listing) and describe how to make bioequivalent analogs at page 8, line 25, *et seq*. The specification teaches what constitutes conservative substitutions, insertions and deletions at page 8, line 32, *et seq*, as well as how to generate muteins of IL-17R proteins (page 9, lines 12-37). Furthermore, the specification teaches what comprises variants of SEQ ID NO:2 and SEQ ID NO:4, as well as how to calculate percent identity and references a well-known and accessible computer program for doing

so (page 10, lines). Additionally, the specification teaches soluble forms of IL-17R at page 4, lines 6-27.

To screen for IL-17R analog proteins that retain the capacity to bind to IL-17, the specification teaches a number of functional screening assays at page 10, lines 21-25, as well as Examples 1 and 2. Therefore, Applicant respectfully submits that identifying IL-17R analogs that are at least 70% identical to the disclosed sequences that retain biological activity, i.e., bind IL-17, is considered routine experimentation. For example, one of skill in the art may perform site-directed mutagenesis on the disclosed IL-17R proteins (disclosed at page 9, lines 30-37) and screen the muteins/variants for the ability to bind to IL-17 or screen the muteins/variants using one of the functional assays mentioned above. Applicant notes that, the skilled artisan would be fully enabled to practice the claimed invention by using techniques known in the art coupled with the specifics given in the specification. Any required experimentation would not be considered *undue* because the art typically engages in such routine experimentation, such as high throughout screening assays for biologically active molecules.

With regards to fragments described in part (d) of claims 14, 17 and 18, Applicant respectfully disagrees with the Examiner's statement that the specification provides no direction, guidance or working example to teach how to make such fragments commensurate with the claimed species. The reasons are essentially the same as presented above. In sum, it would not require undue experimentation to make truncated versions of the extracellular domains of SEQ ID NO:2 or 4, as well as variants thereof, and screen them for the ability to bind IL-17. Applicant has provided the necessary sequences, defined the extracellular regions, described how to determine per cent identity, taught methods of making fragments (e.g., site-directed mutagenesis) and described methods of screening for fragments that bind IL-17. Accordingly, it is a matter of routine experimentation for the skilled artisan to prepare a DNA fragment, express a protein therefrom and determine whether the protein binds IL-17. As such, Applicant respectfully requests that the rejection be properly withdrawn.

Applicant emphasizes that claims to IL-17R polypeptides of comparable scope have been issued in USPN 6,072,033, which shares a common assignee. Therefore, the U.S.P.T.O. has deemed prior applications describing IL-17R polypeptides, variants and fragments thereof as satisfying the enablement requirement. Applicant strongly believes the instant application should be treated similarly.

Finally, Applicant submits that the present specification also enables administering IL-17R to patients. Applicant notes that "[I]f a statement of utility in the specification contains within it a connotation of how to use, and/or the art recognizes that

standard modes of administration are known and contemplated, 35 U.S.C. 112 is satisfied (*In re Johnson*, 282 F.2d 370, 373, 127 USPQ 216, 219 (CCPA 1960)). In fact, "it is not necessary to specify the dosage or method of use if it is known to one skilled in the art that such information could be obtained without undue experimentation." (MPEP 2164.01(c), page 131). A patent need not teach, and preferably omits, what is well known in the art. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991). If one skilled in the art, based on knowledge of compounds having similar physiological or biological activity, would be able to discern an appropriate dosage or method of use without undue experimentation, this would be sufficient to satisfy 35 U.S.C. §112.

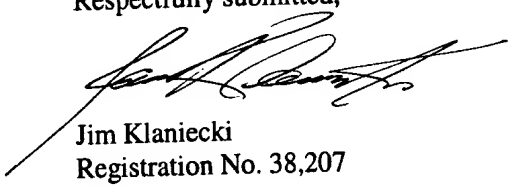
Standard modes of administering molecules such as IL-17R to patients are well known in the art. Applicant notes that other chronic inflammatory diseases have been successfully treated with soluble receptors for proinflammatory cytokines, such as the treatment of rheumatoid arthritis using the TNF receptor (i.e., Enbrel®, Immunex Corp., Seattle, WA). Applicant emphasizes that one of skill in the art would be able to practice the present invention based on Applicant's disclosure because the specification teaches how to make and use IL-17R and standard modes of administering such molecules are known in the art. Consequently, one of skill in the art would not have to perform undue experimentation to practice the claimed methods. Therefore, the rejection under 35 U.S.C. §112, first paragraph should be properly withdrawn.

35 U.S.C. §102(a)

The Examiner has rejected claims 13 and 14 under 35 U.S.C. §102(a) as being anticipated by Yao, et al., WO 96/29408 because he believes the limitation "preventing" would encompass any or all individuals, including the graft recipients in Yao's invention. While Applicant does not acquiesce to the Examiner's characterization, the term "preventing" has been deleted in order to expedite early allowance of the claims. Applicant notes that removal of this additional claim limitation is not considered a narrowing amendment. Therefore, Applicant has obviated the basis for the Examiner's rejection under 35 U.S.C. §102(a) and requests the rejection be properly withdrawn.

Applicant has amended the claims to more particularly point out and distinctly claim what he regards as the invention. No new matter has been added. Applicant respectfully requests amendment of the application and allowance of the claims. The Examiner is invited to contact the undersigned to discuss any remaining issues in order to facilitate early allowance of the application.

Respectfully submitted,



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CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231, on the date indicated below.

Date: Jan. 31, 2002 Signed: Nancy M. Kitson

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the Application of: Anthony B. Troutt

Docket No.: 2623-B

Group Art Unit: 1646

Serial No: 09/488,728

Examiner: D. Jiang

Filed: January 20, 2000

For: METHOD OF REGULATING NITRIC OXIDE PRODUCTION

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

The paragraph at page 4 beginning at line17 has been amended as follows:

The nucleotide and predicted amino acid sequence of the human IL-17R is shown in SEQ ID NOs:3 and 4. It shares many features with the murine IL-17 R. Computer analysis indicated that the protein has an N-terminal signal peptide with a cleavage site between amino acid 27 and 28. Those skilled in the art will recognize that the actual cleavage site may be different than that predicted by computer analysis. Thus, the N-terminal amino acid of the cleaved peptide is expected to be within about five amino acids on either side of the predicted cleavage site. The signal peptide is followed by a 293 amino acid extracellular domain, a 21 amino acid transmembrane domain, and a 525 amino acid cytoplasmic tail. Soluble IL-17R comprises the signal peptide and the extracellular domain (residues 1 to 320 of SEQ ID NO:~~1~~3) or a fragment thereof. Alternatively, a different signal peptide can be substituted for the native signal peptide.

The paragraph at page 16 beginning at line13 has been amended as follows:

The present invention provides methods of using therapeutic compositions comprising an effective amount of a protein and a suitable diluent and carrier. The use of IL-17R or homologs in conjunction with soluble cytokine receptors or cytokines, or other immunoregulatory molecules is also contemplated. Such molecules can be administered separately, sequentially or simultaneously with IL-17R compositions. ~~Particularaly~~

Particularly preferred immunoregulatory ~~moleculs~~ molecules are soluble IL-1 receptors, soluble TNF receptors, and fusion proteins thereof.

In the Claims:

The claims have been amended as follows:

13. (Amended) A method of treating a mammal afflicted with ulcerative colitis, ~~or preventing an inflammatory disease in a mammal,~~ the method comprising administering to said animal an effective amount of ~~an~~ soluble Interleukin-17 Receptor (IL-17R) protein and a pharmaceutically acceptable ~~suitable~~ diluent or carrier~~, wherein the inflammatory disease is selected from the group consisting of ulcerative colitis, diabetes and Crohn's disease.~~

14. (Amended) The method according to claim 13, wherein the soluble IL-17R protein is selected from the group consisting of:

(a) a protein comprising amino acids 1 through 322 of SEQ ID NO:2;

(b) a protein comprising amino acids 1 through 320 of SEQ ID NO:4;

(c) a protein having an amino acid sequence that is at least about 70% identical to the amino acid sequences of the proteins of (a) or (b) ~~as determined using the GAP computer program at default parameters, and~~ that binds IL-17; and

(d) fragments of the proteins of (a), (b) or (c) that bind IL-17.

Kindly add the following new claims:

15. (New) A method of treating a mammal afflicted with diabetes, the method comprising administering to said mammal an effective amount of a soluble Interleukin-17 Receptor (IL-17R) protein and a pharmaceutically acceptable diluent or carrier.

16. (New) The method according to claim 15, wherein the soluble IL-17R protein is selected from the group consisting of:

(a) a protein comprising amino acids 1 through 322 of SEQ ID NO:2;

(b) a protein comprising amino acids 1 through 320 of SEQ ID NO:4;

(c) a protein having an amino acid sequence that is at least about 70% identical to the amino acid sequences of the proteins of (a) or (b) that binds IL-17; and

(d) fragments of the proteins of (a), (b) or (c) that bind IL-17.

17. (New) A method of treating a mammal afflicted with Crohn's disease, the method comprising administering to said mammal an effective amount of a soluble Interleukin-17 Receptor (IL-17R) protein and a pharmaceutically acceptable diluent or carrier.

18. (New) The method according to claim 16, wherein the soluble IL-17R protein is selected from the group consisting of:

(a) a protein comprising amino acids 1 through 322 of SEQ ID NO:2;

(b) a protein comprising amino acids 1 through 320 of SEQ ID NO:4;

(c) a protein having an amino acid sequence that is at least about 70% identical to the amino acid sequences of the proteins of (a) or (b) that binds IL-17; and

(d) fragments of the proteins of (a), (b) or (c) that bind IL-17.